DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO

40th CYCLE
Project proposal for a Sapienza PhD scholarship

Main research line

Title: Role of FBX022 in breast cancer

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Summary (max 500 words)

Ubiquitination is one of the most studied post-translational protein modification and is mediated by ubiquitin proteasome system (UPS) to trigger protein degradation. In general, three enzymes are involved in UPS-induced protein degradation, including ubiquitin activating E1 enzyme, ubiquitin conjugating E2 enzyme, and ubiquitin E3 ligase. The target protein is labeled by ubiquitins and subsequently degraded by the 26S proteasome complex, leading to reduction of substrate proteins. E3 ligases recognize and recruit the target protein for ubiquitination, thus they were extensively characterized. Among E3 ligases, Cullin-RING E3 ligase (CRL) complex is one of the largest families, including CRL1–3, 4A, 4B, 5, 7, and 9. CRL1, also known as SKP1-cullin 1-F-box protein (SCF) E3 ligase complex, contains cullin-1 acting as the scaffold protein, RBX1 for recruiting ubiquitin-loaded E2, SKP1 working as an adaptor protein to connect F-box protein, and F-box protein for selecting substrates for degradation. In humans 69 F-box proteins have been characterized which are divided into three subclasses according to their variable domains: FBXW proteins with WD40 repeat domains, FBXL proteins with leucine-rich repeat domains, and FBXO proteins with other domains like kelch repeats or proline-rich domains.The F-box protein 22 (FBXO22), one of F-box proteins, has been identified to be critically involved in carcinogenesis. FBXO22 promotes proliferation in breast cancer and lung cancer, but suppresses migration and metastasis. FBXO22 exerts oncogenetic functions via promoting the ubiquitination and degradation of its substrates, including KDM4A, KDM4B, methylated p53, p21, KLF4, LKB1, Snail, CD147, Bach1, PTEN, and HDM2. FBXO22 is also regulated by several regulatory factors such as p53, miR-155, SNHG14, and circ_0006282. We recently discovered that in breast cancer cells, besides class 4 histone demethylases KDM4A and KDM4B, FBX022 targets also class 5 KDM5A and KDM5B, qualifying itself as a potential epigenetic regulator. The project aims to correlate the effects of FBX022 on the putative targets with the biological relevant phenotypes in breast cancer cells. At this porpoise, we will make use of a system to deplete (siRNAs) or over-produce (expression plasmid) the protein in different breast cancer cell lines. The effects on the relevant protein targets will be verified by western blot and mass spectrometry and parameters of vitality, cell migration, invasion and sensitivity to genotoxic damage will be analyzed. We also plan to monitor the effects on histone modifications.

Pertinent Publications of the proponent (last 5 years)

- Abdul Rehman SA, Cazzaniga C, Di Nisio E, Antico O, Knebel A, Johnson C, Şahin AT, Ibrahim PEGF, Lamoliatte F, Negri R, Miratul Muqit MK, De Cesare V. (2024). Discovery and characterization of noncanonical E2-conjugating enzymes. SCIENCE ADVANCES, vol. 10, ISSN: 2375-2548, doi: 10.1126/sciadv.adh0123

- Di Nisio E, Licursi V, Mannironi C, Buglioni V, Paiardini A, Robusti G, Noberini R, Bonaldi T, Negri R (2023). A truncated and catalytically inactive isoform of KDM5B histone demethylase accumulates in breast cancer cells and regulates H3K4 tri-methylation and gene expression. CANCER GENE THERAPY, ISSN: 0929-1903, doi: 10.1038/s41417-022-00584-w.

- Frigerio C, Di Nisio E, Galli M, Colombo CV, Negri R, Clerici M (2023). The chromatin landscape around DNA double-strand breaks in yeast and its influence on DNA repair pathway choice. INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES, vol. 24, p. 1-24, ISSN: 1422-0067, doi: 10.3390/ijms24043248.

-Di Nisio E, Lupo G, Licursi Va, Negri R (2021). The Role of Histone Lysine Methylation in the Response of Mammalian Cells to Ionizing Radiation. FRONTIERS IN GENETICS, 12: 1664-8021.

-Pippa S, Mannironi C, Licursi V, Bombardi L, Colotti G, Cundari E, Mollica A, Coluccia A, Naccarato V, La Regina G, Silvestri R, Negri R (2019). Small molecule inhibitors of KDM5 histone demethylases increase the radiosensitivity of breast cancer cells overexpressing Jarid1b. MOLECULES 24: pii: E1739.

-Mocavini I, Pippa S, Licursi V, Paci P, Trisciuoglio D, Mannironi C, Presutti C, Negri, R (2018). JARID1B expression and its function in DNA damage repair are tightly regulated by miRNAs in breast cancer. CANCER SCIENCE 110:1232-1243.

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-Li, S., He, J., Liao, X. et al. Fbxo22 inhibits metastasis in triple-negative breast cancer through ubiquitin modification of KDM5A and regulation of H3K4me3 demethylation. Cell Biol Toxicol 39, 1641–1655 (2023). https://doi.org/10.1007/s10565-022-09754-w.

-Tan MK, Lim HJ, Harper JW. SCF(FBXO22) regulates histone H3 lysine 9 and 36 methylation levels by targeting histone demethylase KDM4A for ubiquitin-mediated proteasomal degradation. Mol Cell Biol. 2011 Sep;31(18):3687-99. https://doi.org/10.1128/MCB.05746-11

-Johmura Y, Maeda I, Suzuki N, Wu W, Goda A et al., Fbxo22-mediated KDM4B degradation determines selective estrogen receptor modulator activity in breast cancer. Clin Invest. 2018;128(12):5603-5619. https://doi.org/10.1172/JCI121679.

-Cheng, J., Lin, M., Chu, M. et al. Emerging role of FBXO22 in carcinogenesis. Cell Death Discov. 6, 66 (2020). https://doi.org/10.1038/s41420-020-00303-0

-De S, Holvey-Bates EG, Mahen K, Willard B, Stark GR. The ubiquitin E3 ligase FBXO22 degrades PD-L1 and sensitizes cancer cells to DNA damage. Proc Natl Acad Sci U S A. 2021 Nov 23;118(47):e2112674118. https://doi.org/10.1073/pnas.2112674118